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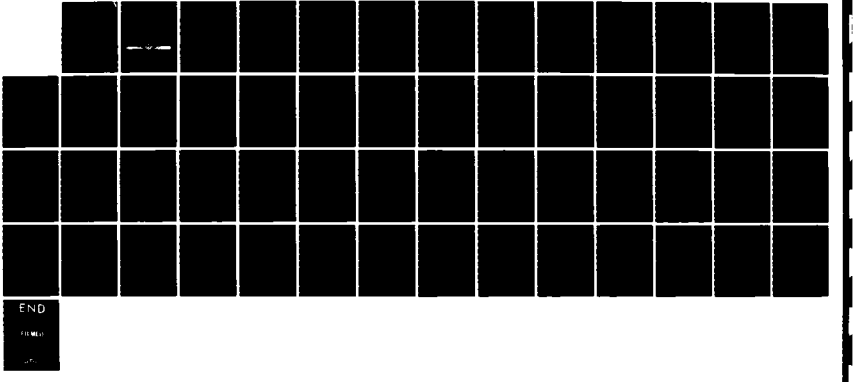

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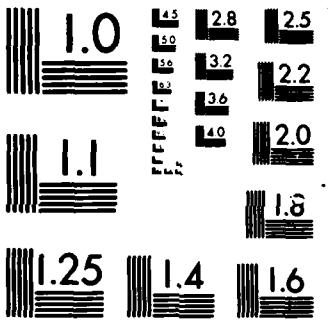

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REPORT NO. T12/85

ATROPINE AND THERMOREGULATION IN MAN (A REPORT OF THREE STUDIES)

US ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE
Natick, Massachusetts

JUNE 1985

UNITED STATES ARMY
MEDICAL RESEARCH & DEVELOPMENT COMMAND

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This report summarizes the findings of three studies which concerned atropine-impaired thermoregulation in male soldiers who exercised in hot environments. Study I examined the effects of field applicable doses (2, 4 mg im.) of atropine on soldiers in fatigue uniforms who walked in a hot-dry (40°C/20% rh) environment; the gradation of these effects with increased dosage (0, 0.5, 1, 2 and 4 mg); and the repeatability of responses to a 2 mg dosage. Study II examined the effects of heat acclimation on atropinized subjects (2 mg im.) during an exercise-heat exposure (49°C/20% rh), and discussed some advantages

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conferred by heat acclimation, including increased total body sweating rate and prolonged work time. Study III examined the effects of three different environmental conditions (42°C/20% rh, 34°C/55% rh, 30°C/70% rh) on exercise performance and heat transfer following atropine (2 mg im.). Conclusions for Study I indicate that the relationship between atropine dose and heart rate (HR) is curvilinear (HR plateaued as dose increased) while the relationship with rectal temperature (T_{re}) is linear; 0.5 mg atropine resulted in increased HR and mean weighted skin temperature (T_{sk}); and T_{re} was unaffected by previous days of atropine administration. Study II demonstrated that heat acclimation improved the endurance time of atropine-treated subjects in a hot-dry environment, due in part to potentiation of sweat gland activity enabling greater evaporative cooling. Study III demonstrated that performance time was not reduced in atropine-treated subjects in the more humid environments, due most probably to dry heat loss, and less reliance on evaporative heat loss to maintain body temperature.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR. 70-25 and USAMRDC Regulation 70-25 for use of volunteers in research.

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TECHNICAL REPORT
No. 12/85

ATROPINE AND THERMOREGULATION IN MAN

(A Report of Three Studies)

by

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June 1985

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PREFACE

The methodology and findings of these studies as described (and referenced) in this report have been published in the open literature as follows:

Kolka, M.A., W. L. Holden and R.R. Gonzalez. Heat exchange following atropine injection before and after heat acclimation. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 56(4):896-899, 1984.

Kolka, M.A., L. Levine, B.S. Cadarette, P. B. Rock, M. N. Sawka and K.B. Pandolf. Effect of heat acclimation on atropine-impaired thermoregulation. Avait. Space Environ. Med. 55:1107-1110, 1984.

Levine, L., M. N. Sawka, B.E. Joyce, B.S. Cadarette and K.B. Pandolf. Varied and repeated atropine dosages and exercise-heat stress. Eur. J. Appl. Physiol. 53:12-16, 1984.

Sawka, M.N., L. Levine, M.A. Kolka, B.S. Appleton, B.E. Joyce and K.B. Pandolf. Effect of atropine on the exercise-heat performance of man. Fundam. Appl. Toxicol. 4:S190-S194, 1984.

Also from these studies, the following manuscripts have been submitted for publication in the open literature:

Cadarette, B.S., L. Levine, L.A. Stephenson, P.B. Rock and M.A. Kolka. Thermoregulatory responses to exercise of atropine-treated men in varied environments.

Gonzalez, R.R., M.A. Kolka and L.A. Stephenson. Effect of atropine on local skin wettedness and sensible heat loss.

Kolka, M.A. and L.A. Stephenson. Environmental stress after atropine treatment.

TABLE OF CONTENTS

LIST OF FIGURES

Figure Legends Continued

LIST OF TABLES

ABSTRACT

This report summarizes the findings of three studies which concerned atropine-impaired thermoregulation in male soldiers who exercised in hot environments. Study I examined the effects of field applicable doses (2, 4 mg im.) of atropine on soldiers in fatigue uniforms who walked in a hot-dry (40°C/20% rh) environment; the gradation of these effects with increased dosage (0, 0.5, 1, 2 and 4 mg); and the repeatability of responses to a 2 mg dosage. Study II examined the effects of heat acclimation on atropinized subjects (2 mg im.) during an exercise-heat exposure (49°C/20% rh), and discussed some advantages conferred by heat acclimation, including increased total body sweating rate and prolonged work time. Study III examined the effects of three different environmental conditions (42°C/20 % rh, 34°C/55% rh, 30°C/70% rh) on exercise performance and heat transfer following atropine (2 mg im.). Conclusions for Study I indicate that the relationship between atropine dose and heart rate (HR) is curvilinear (HR plateaued as dose increased) while the relationship with rectal temperature (T_{re}) is linear; 0.5 mg atropine resulted in increased HR and mean weighted skin temperature ($\bar{T}_{sk}$); and T_{re} was unaffected by previous days of atropine administration. Study II demonstrated that heat acclimation improved the endurance time of atropine-treated subjects in a hot-dry environment, due in part to potentiation of sweat gland activity enabling greater evaporative cooling. Study III demonstrated that performance time was not reduced in atropine-treated subjects in the more humid environments, due most probably to dry heat loss, and less reliance on evaporative heat loss to maintain body temperature.

Key Words: atropine sulfate, exercise in the heat, heat acclimation, heart rate, rectal temperature, sweating rate.

INTRODUCTION

Atropine sulfate (atropine) acts as a competitive antagonist to the neurotransmitter acetylcholine (ACh), where it binds to the ACh receptor sites of effector organs, blocking the muscarinic effects normally exerted by ACh. Atropine's effects include the prevention of ACh from acting on smooth muscle, heart and exocrine glands (28). For eccrine sweat glands (innervated via sympathetic cholinergic fibers primarily by ACh), the result of this competitive inhibition is reduced thermoregulatory sweating (6,30).

Soldiers are authorized to carry and, when directed, self-administer the drug atropine for treatment of anticholinesterase (organophosphate) nerve agent poisoning. During combat it is possible that atropine could inadvertently be used in the absence of a nerve agent challenge, as during a false alarm or confusion about a possible alarm. Because of its thermoregulatory effects, it is this condition of inappropriate atropine administration that concerns us in our investigations.

It has been reported that atropine administration will reduce exercise time and elevate heart rate and core temperature during exercise and/or heat stress (7,9,10,11,34). However, data from these studies are difficult to intergrate for military use because of methodological differences between studies and/or non-relevant testing scenarios. Cullumbine et al. (10) have studied the effects of repeated dosages of 2 and 5 mg (im.) atropine for men at rest. That study was conducted in a comfortable environment, and the atropine treatment did not elicit thermal strain. Since atropine causes profound thermoregulatory impairment (34), the need remained to conduct varied and repeat dosage tests during exercise in the heat.

Heat acclimation enhances the responsiveness of the eccrine sweat glands to a given amount of ACh (6,14), which may be the reason for the potentiation of sweat gland activity seen after acclimation to dry heat (13). Heat acclimation enables a subject to complete a given exercise-heat stress with less thermal and cardiovascular strain and to extend tolerance time. For atropinized subjects, heat acclimation may also enhance tolerance to exercise-heat stress.

For soldiers working in a desert-like environment which does not facilitate dry heat loss (e.g. skin temperature close to ambient temperature), the evaporation of eccrine sweat gland secretion provides the major defense against heat storage. When the heat load of metabolism and the environment exceeds the body's ability to dissipate heat by evaporation, due to either an insufficiency of sweating or a decrease in the evaporative capacity of the environment (e.g. high humidity), core and skin temperatures rise above expected levels determined by work intensity and ambient temperature (17). During these conditions, the decreased sweating and excess heat storage (8,20,24) would lead to decreased work performance and possible heat casualties (25,34). Atropinized subjects performing exercise in hot-dry environments would be most susceptible to thermoregulatory impairment. The extent of impairment for atropinized subjects in environments having similar wet bulb globe temperatures (WBGT) but different evaporative capacities had not been determined prior to these investigations.

The three studies undertaken thus far have been designed to address some of these problems and will be used to clarify the larger picture of (organophosphate) agent/antidote effects on thermoregulatory and exercise performance parameters in man.

The purposes of the three studies are as follows:

Study I. The purpose of the first study was to determine the physiological effects (HR, T_{re}, $\bar{T}_{sk}$) of field applicable doses (2 and 4 mg im.) of atropine on soldiers dressed in Temperate Battle Dress Uniforms (TBDU), exercising in a hot-dry environment. We also wanted to determine the gradation of these effects with increasing doses (0.5, 1, 2, 4 mg im.), and to test the repeatability of physiological responses to repeat trials of 2 mg dosages of atropine.

Study II. It was the purpose of the second study to examine the effects of heat acclimation on the reduced sweating rate that occurs following atropine administration. The data obtained has been helpful in determining that further research on atropine's suppression of sweating should control for acclimation state.

Study III. The purpose of the third study was to examine the effects of three similar environmental conditions (WBGT) with different evaporative capacities on exercise performance and heat transfer following atropine administration. Specifically, an evaluation of local and whole body sweating and the relationship of thermoregulatory sweating to body temperature as well as the alteration of the relationship was evaluated for the three environmental conditions following atropine injection. These data have also been used to evaluate skin wettedness in the six conditions.

Military Relevance

The US Army must be prepared to engage in military operations under varied environmental conditions. During these operations, soldiers will engage in a variety of tasks involving physical exercise. It is well established that there are exercise performance decrements in hot compared to thermal neutral environments. Furthermore, if a chemical agent were to be introduced into a hot environment, either the use of protective clothing (MOPP) or a pharmaceutical antidote (such as atropine) would result in further performance decrements.

These studies were designed to expand our data base on the physiological effects of various doses of atropine administration in the absence of organophosphate nerve agent, acclimation state on soldiers treated with atropine especially with regard to suppression of sweating, and atropine administration on the performance of soldiers exposed to different environmental stresses.

Minimizing Risk to Subjects

Except for the intramuscular administration of atropine , most of the procedures in the three studies fell within the framework, restrictions and safety limitations of the Type Protocols for: Human Research Studies of Thermal Stress; and Exercise and Physical Training (MAR 1984*).

*Approved 5 March 1984. The Type Protocol provides information and explanations about conditions, standards and safeguards, in order to serve as an encompassing framework for specific in-house studies in its general subject area. It is to be used as a reference to facilitate the understanding and review of specific study protocols which conform to its provisions, and thus do not exceed the degree of risk, and safety limits herein stipulated (reference para 19, USAMRDC Reg 70-25, 27 April 1981).

To minimize risks associated with atropine, volunteers were given medical examinations and psychological screening tests prior to acceptance as subjects. No one with a history of asthma, glaucoma or intraocular injury, peptic ulcer, or adverse reactions to previous atropine administration (as in the form of eye drops, antispasmodics or decongestants) was used as a subject. Fatalities from atropine alone are rare; the lethal dose is unknown. (It may be as low as 65 mg for some individuals, or greater than 1000 mg for others). Central nervous system manifestations (emotional instability, anxiety, hallucinations, etc.) are usually absent or mild with less than 5 mg dosages. Fatigue, headache, lightheadedness and incoordination can be expected in at least 25% of subjects receiving a 2 mg dosage.

METHODS AND RESULTS

STUDY I

Methods

Subjects. Seven healthy male soldiers served as volunteer test subjects for this study after receiving physical examinations and signing a statement of informed consent. The physical characteristics of the subjects were ($\bar{X} \pm SD$): age, 24 $\pm$ 3 years; height, 174 $\pm$ 12 cm; weight, 76 $\pm$ 3 kg; and body fat, 15 $\pm$ 2% (12).

Experimental Design. All testing was conducted during September and October in Natick, Massachusetts when subjects were naturally partially heat acclimatized. In addition, subjects were acclimated in an environmental chamber for four days before testing. Environmental chamber conditions were: dry bulb temperature (T_{db}) 40°C, dew point temperature (T_{dp}) 19°C, and relative humidity (rh) 30%. Acclimation consisted of two 50-min exercise bouts of level treadmill walking (1.34 $m \cdot s^{-1}$), each preceded by a 10-min rest. During acclimation subjects wore shorts, T-shirts and tennis shoes.

Following acclimation, 8 test days in the heat (T_{db} = 40°C, T_{dp} = 13°C, rh= 20%), alternating with rest days (no drug or heat exposure to diminish the possibility of a cumulative drug effect or tolerance), were conducted while subjects exercised the same as during acclimation. The 1st, 4th and 7th test days served as controls; subjects received a placebo injection of normal saline. Test days 2, 3, 5 and 6 were atropine treatment days of 0.5, 1,2 and 2 mg, respectively. On test day 8, varied dosages from 0.5 to 4 mg atropine were

administered. The five atropine exposures were tested in progressive order from 0.5 to 4 mg so that subjects who were unable to tolerate a low dose would not be exposed to a higher dose. Except for the increased physiological responses to the heat stress, none of the subjects exhibited adverse reactions. However, only two subjects volunteered to be tested with the 4 mg dose of atropine.

On the test days subjects were dressed in TBDUs. These uniforms have a total insulation value of 1.49 clo, and a moisture permeability index of 0.39 (41). Baseline HR, T_{re} and $\bar{T}_{sk}$ were recorded while subjects were seated in a comfortable antechamber (T_{db} = 20°C, T_{dp} = 6°C, rh= 40%). Following baseline measurements, placebo or atropine injections were administered (vastus lateralis muscle). Within 10 min subjects entered the heated chamber where two cycles of 10-min rest and 50-min exercise were attempted. During rest and exercise, subjects were asked to rate their perception of effort (RPE) by the method of Borg (1) and their thermal sensation (TS) as described by Gagge et al. (16). Throughout acclimation and testing, subjects were allowed to drink water ad libitum. Testing was terminated for any subject whose T_{re} reached 39.5°C, whose HR exceeded 180 bt·min^{-1} for 5 min, who requested withdrawal, or who was removed at the discretion of the medical monitor.

On each day, physiological data obtained were: HR from ECG chest electrodes (CM5 placement); T_{re} from a thermistor probe (Yellow Springs Instrument Co., Inc., USA) inserted approximately 10 cm beyond the anal sphincter; and $\bar{T}_{sk}$ (4), using a three-point thermocouple skin harness (chest, calf and forearm). Heart rates were continuously radio-telemetered to an oscilloscope tachometer (Hewlett-Packard). Rectal and skin temperatures were

recorded and plotted continuously (Hewlett-Packard-9825B calculator and 9872A plotter). To determine metabolic cost, expired air samples were analyzed during rest and exercise. Oxygen uptake and respiratory exchange ratio were used to calculate energy cost (40).

Statistical Analysis. A 3-way ANOVA with repeated measures was employed for comparisons of HR, T_{re} and $\bar{T}_{sk}$ among four treatments (0, 0.5, 1 and 2 mg atropine) for seven subjects at six times (baseline, pre-exercise, 20 min and 50 min of exercise bout 1, and 20 min and 50 min of exercise bout 2). An ANOVA was also employed to compare metabolic measurements, RPE and TS, and for comparisons of HR and T_{re} between the two 2 mg treatment days and among the three control days.

Results

Physiological data from the fourth acclimation day were very similar to data observed for the three control days, indicating that heat acclimation was complete by the fourth day. For the examined physiological variables statistical comparisons among the three control days showed no significant differences ($P>0.05$) and day four, randomly chosen as representative of the control condition, was used in the comparisons among treatments. Of the two 2 mg atropine treatment days, day six, the second 2 mg exposure, was chosen for the comparisons among doses because one subject did not test on day five. During the first 2 mg atropine exposure, testing was terminated for three subjects whose T_{re} were 39.5°C, ~25 min into the second exercise bout (105 min post injection). During the second 2 mg exposure, testing was terminated for two of the same three subjects whose T_{re} were also 39.5°C, 25 and 40 min into the second exercise bout (105 and 120 min post injection). For this reason, the

comparisons between the 2 mg trials were made only to 20 min into the second exercise bout (100 min post injection), when all subjects were still exercising. For the comparisons among the varied treatments, final data points in the 2 mg trial (HR, T_{re}, $\bar{T}_{sk}$) were estimated for two subjects (38). The two subjects who received 4 mg of atropine on test day eight were able to complete only one exercise bout. Metabolic cost for all trials was approximately 140 W at rest and 390 W during exercise.

As illustrated in Figure 1 in all trials, HR increased from rest to exercise. While HR during exercise was similar over time in the control trial, all atropine treatments caused further increases ($P<0.01$) in HR by the end of the first exercise bout. Thereafter, for each trial HR remained unchanged during exercise. At the end of each exercise bout HR was significantly elevated ($P<0.01$) with each increasing atropine dosage. Peak values were recorded at *min 50.*

Rectal temperature, presented in Figure 2, increased by the end of the first exercise bout during all treatments. During the 2 mg trial, T_{re} continued increasing throughout the second exercise bout ($P<0.01$), and by the end of exercise, it was 0.9°C higher than during the 1 mg trial, which itself was 0.3°C higher than during the 0.5 mg and control trials ($P<0.01$).

Skin temperature varied with treatment, but was generally higher ($P<0.01$) with each increasing dosage (Fig. 3). In the control trial the initiation of exercise caused a significant decline in $\bar{T}_{sk}$, which remained stable thereafter. During the 0.5 mg trial $\bar{T}_{sk}$ did not change with exercise, while in both the 1 and 2 mg trials it increased with the onset of exercise and remained stable thereafter. By the first 20 min of exercise, $\bar{T}_{sk}$ was higher during the 2 mg trial than during all other trials ($P<0.01$).

Neither atropine nor placebo treatment affected RPE during rest or exercise ($P>0.05$). The overall mean RPE was 8.9 ± 1.2 during rest, and 11.0 ± 0.9 during exercise. Thermal sensation however was affected by treatments. At rest, TS during the 2 mg trial (5.9 ± 0.3) was greater ($P<0.05$) than during the control trial (5.1 ± 0.2). During exercise, TS during the 2 mg trial (5.8 ± 0.2) was greater ($P<0.05$) than the control (5.4 ± 0.2) and 0.5 mg (5.5 ± 0.2) trials.

Figure 4 illustrates the curvilinear relationship for HR and the linear relationship for T_{re} when these responses are regressed against the various atropine dosages for the two subjects who were tested with all four dosages. Skin temperatures for these subjects also increased proportionally to atropine dosage. At 50 min of exercise $\bar{T}_{sk}$ was 34.1, 34.9, 35.3, 36.2 and 38.8°C for the control trial, 0.5, 1, 2 and 4 mg atropine trials, respectively.

Statistical comparisons between the two 2 mg treatment days were made for HR and T_{re} for six subjects (Fig. 5). Overall mean HR was about 5% lower on the second 2 mg treatment day compared to the first at 115 ± 14 and 121 ± 15 bt·min $^{-1}$, respectively ($P<0.01$). Rectal temperature was the same (37.6°C, $P>0.05$) throughout exercise on both days.

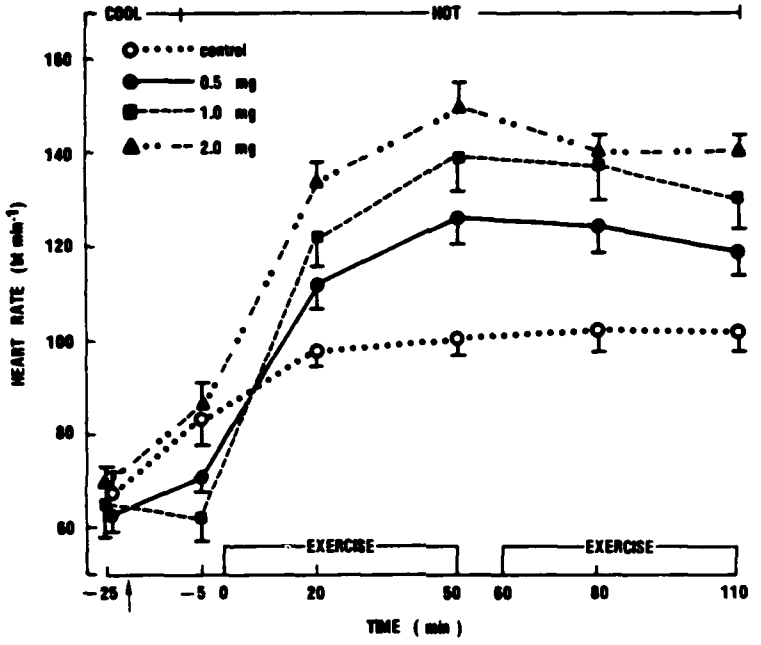

Figure 1. Heart rates ($\bar{X} \pm SE$) during rest in cool (20°C, 40% rh) and hot (40°C, 20% rh) environments and during two exercise bouts in the heat for control, 0.5, 1 and 2 mg atropine treatments. The arrow indicates the time of injection (n=7).

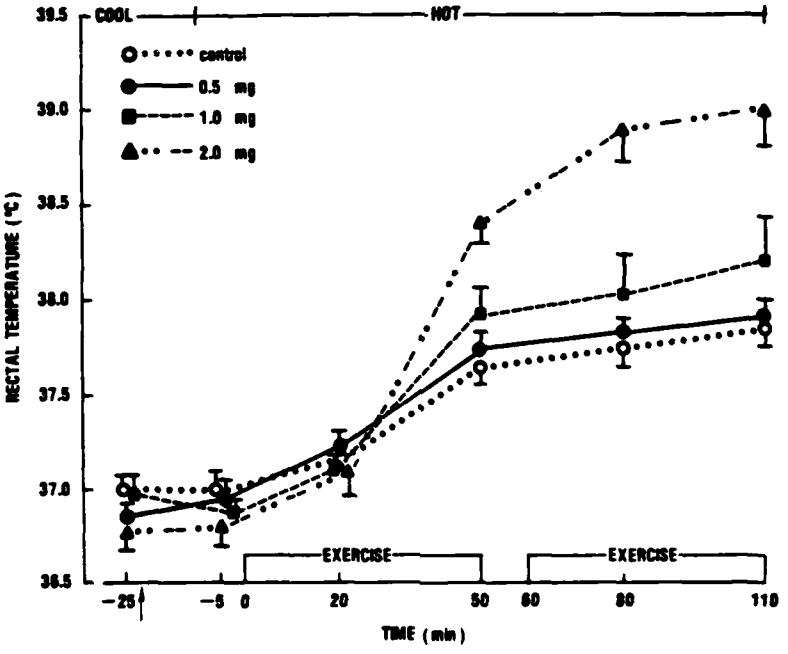

Figure 2. Rectal temperatures for conditions as described in figure 1 (n=7).

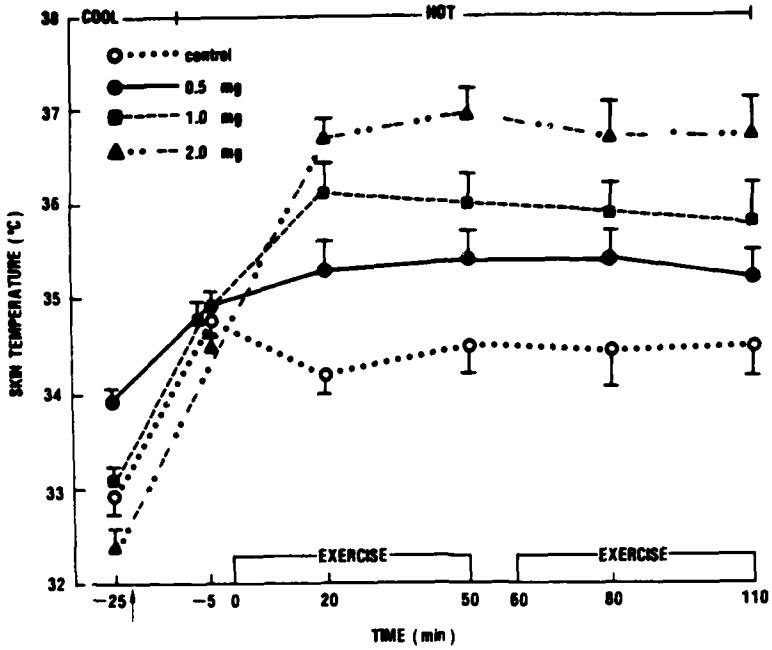

Figure 3. Mean weighted skin temperatures for conditions as described in figure 1 (n=7).

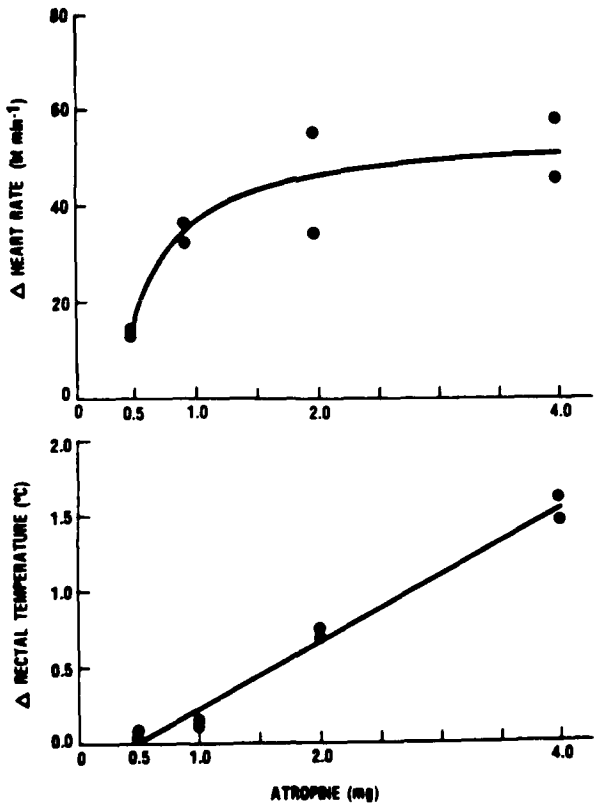

Figure 4. The change (Δ) in heart rate and rectal temperature between atropine and control treatments at 50 min of exercise, plotted against atropine dosage (n=2).

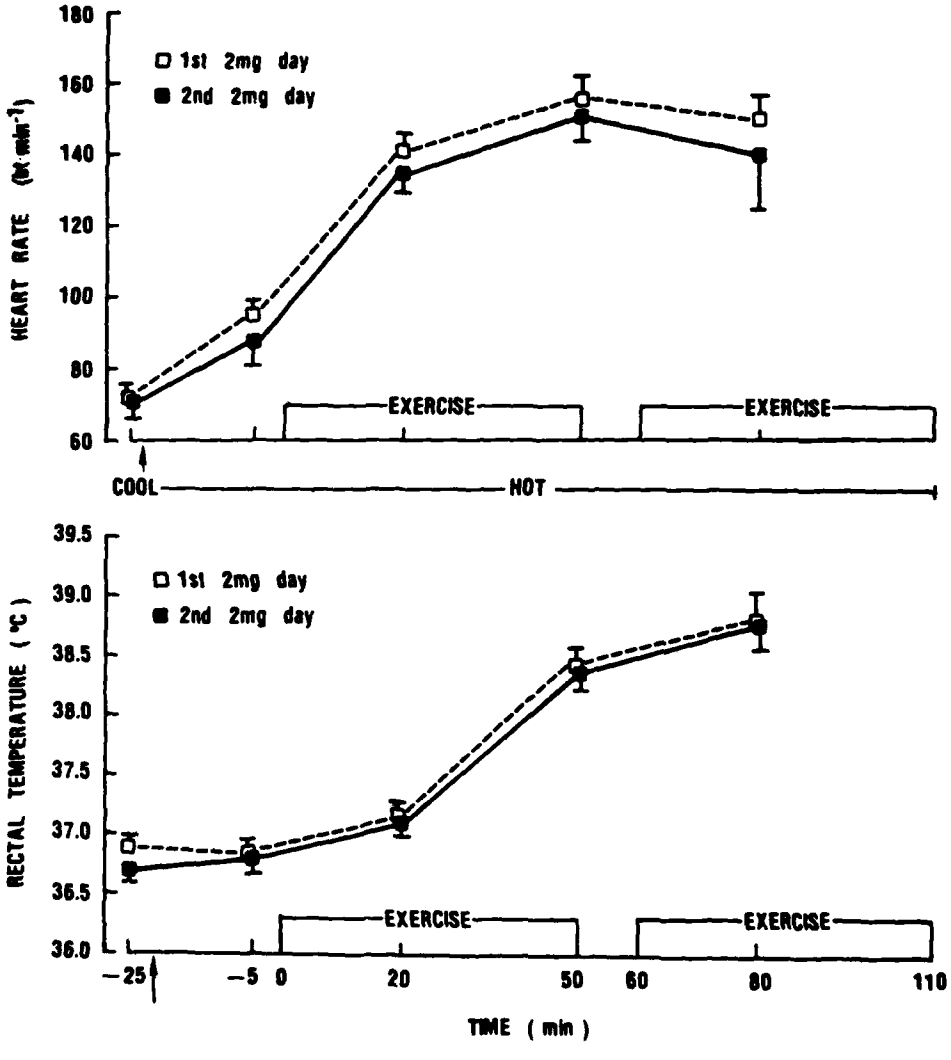

Figure 5. Heart rates and rectal temperatures ($\bar{X} \pm SE$) during rest and exercise for the 1st (day 5) 2 mg and 2nd (day 6) 2 mg atropine treatment days (n=6).

STUDY II

Methods

Subjects. Seven healthy male volunteers participated as test subjects in this investigation after giving their informed consent. The subjects had a mean ($\pm$ SD) age of 22 $\pm$ 3 years, weight of 79.9 $\pm$ 9.8 kg, Dubois body surface area of 2.02 $\pm$ 0.16 m^2, and percent body fat (12) of 14.6 $\pm$ 4.6%. Their mean maximal aerobic power was 50.2 $\pm$ 6.0 $ml \cdot kg^{-1} \cdot min^{-1}$.

Experimental Design. The subjects were tested on four separate occasions: two times prior to a heat acclimation program and two times after completion of that program. The testing consisted of an exercise-heat exposure (T_{db} = 49°C, T_{dp} = 20°C, rh = 20%) in which the subjects walked (1.34 $m \cdot s^{-1}$) on a level, motor-driven treadmill for a prolonged period (4 repeats of 10 min rest and 25 min exercise) or until T_{re} reached 39.5°C, HR exceeded 180 $bt \cdot min^{-1}$ for 5 min, or the subject voluntarily terminated the exercise-heat exposure. During the exposures, T_{re} and $\bar{T}_{sk}$ (3) ($\bar{T}_{sk}$; chest, arm, calf), HR and assessment of TS (16) were monitored. Metabolic heat production (M) was calculated during each 25-min period from open-circuit spirometry measurements. Subjects drank water ad libitum during all heat exposures. Total body sweating rates ($\dot{M}_{sw}$) were determined from body weight changes, corrected for water ingested, measured on a Sauter balance each 25-min period. $\dot{M}_{sw}$ was corrected for evaporative and convective loss from the respiratory tract (15,23).

Each subject completed two exercise-heat exposures during the pre-acclimation period. On one occasion, 2 mg of atropine was injected into the vastus lateralis muscle immediately before the subject entered the

environmental chamber (15 min before the onset of exercise). On the other pre-acclimation exposure, subjects were injected with an identical volume (1 ml) of normal saline as a control. These exposures were randomized and separated by two days to avoid effects of consecutive days of heat exposure.

After the pre-acclimation tests, the subjects completed a 10-day heat acclimation program (T_{db} = 49°C, T_{dp} = 20 °C, rh = 20%). During this program, they walked on a level treadmill at 1.34 $m \cdot s^{-1}$ for 2 repeats of 10 min rest followed by 50 min exercise (120 min total) or until voluntary termination. Heat acclimation was defined by equivalent T_{re} and HR on two consecutive acclimation days.

The post-acclimation testing was identical to the pre-acclimation testing. The subjects were tested on two occasions, once after atropine (2 mg) administration and once as a control after the injection of an equal volume of saline. These exposures were randomized and separated by one day to maintain the level of heat acclimation.

The increase in heat content (ΔQ) during the exercise-heat exposure was calculated as $\Delta Q = (\Delta T_{re}/\ \Delta t\ (60 \cdot 0.97\ m_b)/A_D (W \cdot m^{-2})$, where $\Delta T_{re}/\Delta t$ is the change in rectal temperature per min, 0.97 is the specific heat content of the tissues ($W \cdot h^{-1}/kg^{-1} \cdot {}^{o}C^{-1}$), m_b is the lean body mass (kg), and A_D is the Dubois surface area (m^2).

Statistical Treatment. Exposure times for the pre-and post- acclimation atropine experiments were compared by paired t-tests. A 3-way analysis of variance (39) was utilized for all data at the time of peak drug effects (30 min post-injection) (27) when a complete heat balance could be determined (22). Linear regression coefficients were calculated for ΔQ and T_{re} over time. An analysis of variance of the slopes of the regression lines, T_{re} vs. time and ΔQ

vs. time, for the four treatments was performed (2). Post-hoc comparisons were accomplished by the Tukey-Kramer method (39). Stepwise regressions of T_{re}, exposure time and TS were evaluated (39). Data presented are means $\pm$ SD.

Results

All seven subjects were able to complete the control exercise-heat exposure both pre- and post-heat acclimation. For the control tests heat acclimation resulted in significant decreases in final exercise T_{re} (0.4°C, $P<0.05$), and final exercise HR (17 bt·min^{-1}, $P < 0.05$), and significantly increased $\dot{M}_{sw}$ (0.54 g·min^{-1}, $P < 0.05$). Post-acclimation subjects drank more water ($P<0.05$) during both the control (Δ 383 ml) and atropine (Δ 176 ml) exercise-heat exposures.

Exposure time increased by an average of 23.5 min (from 56.5 to 80.0 min) during atropine tests post-acclimation ($P<0.08$). Pre-acclimation, after atropine injection, exercise was terminated by high T_{re} (39.5°C) in three subjects, high HR (>180 bt·min^{-1}) in two subjects, and syncope in the remaining two subjects. After acclimation, exposure time was limited by elevated T_{re} in two subjects, high HR in three subjects, while two subjects completed the 140 min of exercise-heat exposure after atropine injection.

Table 1 illustrates the mean data ($\pm$ SD) for the subjects at the 30th min of exercise-heat exposure pre- and post-acclimation. This time was chosen, as it is the last point in the experiment that all data necessary for a complete thermal evaluation of the seven subjects were obtained under all four test conditions (due to differences in individual subject performance time). Additionally, the peak effect of atropine on sweat gland inhibition occurred at 30 min of exercise. The effects of atropine injection are clearly evident by the decreased $\dot{M}_{sw}$ and

increased T_{re} and $\bar{T}_{sk}$ compared to saline injections. Atropine reduced pre-acclimation $\dot{M}_{sw}$ by 5.08 $g \cdot min^{-1}$; however, atropine reduced $\dot{M}_{sw}$ by only 3.37 $g \cdot min^{-1}$ after heat acclimation ($P<0.05$).

Table 1. Mean (± SD) values for seven male subjects at the 30th minute of heat exposure

	T_{re} (°C)	$\bar{T}_{sk}$ (°C)	M ($W \cdot m^{-2}$)	$\dot{M}_{sw}$ ($g \cdot min^{-1}$)	HR ($bt \cdot min^{-1}$)
Pre-acclimation					
Contol	37.4	35.9	185	9.43	110
	(0.2)	(0.9)	(24)	(1.82)	(9)
Atropine	37.8**	38.7**	195	4.34**	163**
	(0.6)	(0.7)	(27)	(0.77)	(13)
Post-acclimation					
Control	37.2	36.0	174	10.34**	98
	(0.2)	(0.8)	(19)	(1.31)	(13)
Atropine	37.7	38.0***	185	6.97***	160
	(0.2)	(0.7)	(22)	(2.12)	(16)

**Significantly different from pre-acclimation control ($p < 0.01$)

***Significantly different from pre-acclimation atropine ($p < 0.01$)

Heat acclimation increased $\dot{M}_{sw}$ ($P<0.05$) during both control (0.91 $g \cdot min^{-1}$) and atropine (2.63 $g \cdot min^{-1}$) exercise-heat exposures. Table 2 clearly demonstrates that heat acclimation elevated $\dot{M}_{sw}$ for most subjects during both the atropine and control tests. There was no interaction between the acclimation effect and the drug effects for any of the examined variables. The time course of the heart rate responses for the atropine exposures is shown in

Figure 6, and rectal temperature responses in Figure 7. Regression analyses of portions of the individual rectal temperature lines during peak drug effects (min 24-34) illustrate that the change in rectal temperature ($\Delta Tre/\Delta t$) was significantly higher ($P< 0.05$) after atropine than saline administration both before and after heat acclimation. Analysis of variance of the rate of rise in rectal temperature, pre- and post-acclimation in atropine-injected subjects, indicated a significantly lower ($P< 0.05$) rectal temperature response following acclimation. As would be predicted from the increased rate of change in T_{re}, the increase in heat content (Table 3) was significantly greater ($P<0.05$) in the atropine-treated individuals both pre- and post-acclimation.

Table 2. Individual total body sweat loss ($\dot{M}_{sw}$; $g \cdot min^{-1}$) at 30 min of exercise-heat exposure, pre- and post-acclimation

Subject	Control		Atropine	
	Pre	Post	Pre	Post
1	9.39	9.96	7.20	6.34
2	7.76	8.76	2.36	2.59
3	11.75	11.50	3.23	7.52
4	6.85	7.50	3.33	4.58
5	11.14	11.04	8.35	8.42
6	9.00	12.34	4.88	10.09
7	9.68	11.09	1.31	9.82

Table 3. The mean (± SD) change in heat content ($W \cdot h \cdot m^{-2}$) at minutes 14 to 24 of exercise pre-and post-acclimation

Pre-acclimation		Post-acclimation	
Control	Atropine	Control	Atropine
39.8 ± 10.1	100.9 ± 18.7*	36.0 ± 12.3	92.8 ± 21.3*

*Significantly different ($p < 0.01$) from control

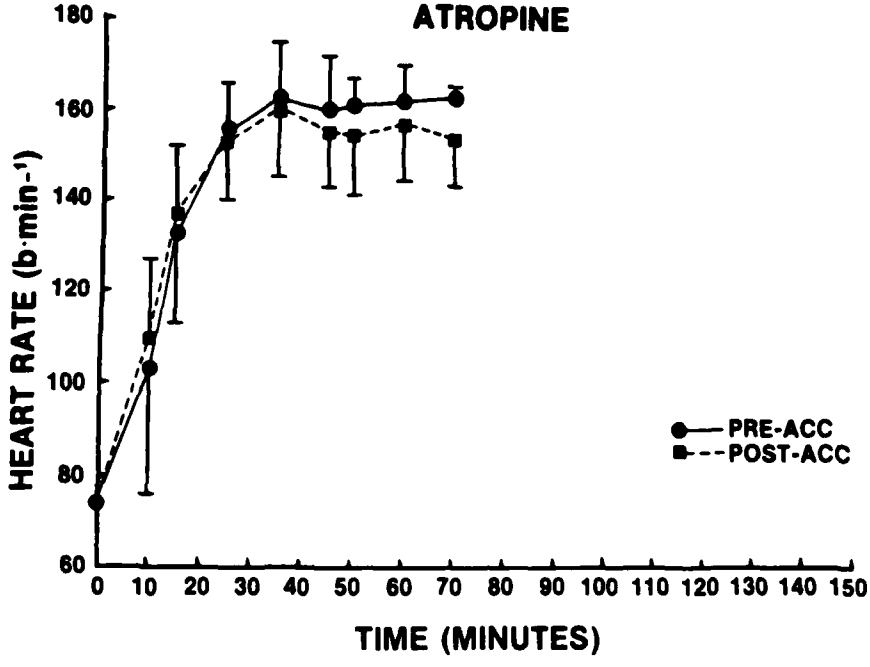

Figure 6. Heart rates ($\bar{X} \pm SD$) after injection of 2 mg atropine both pre- and post-heat acclimation (n=7).

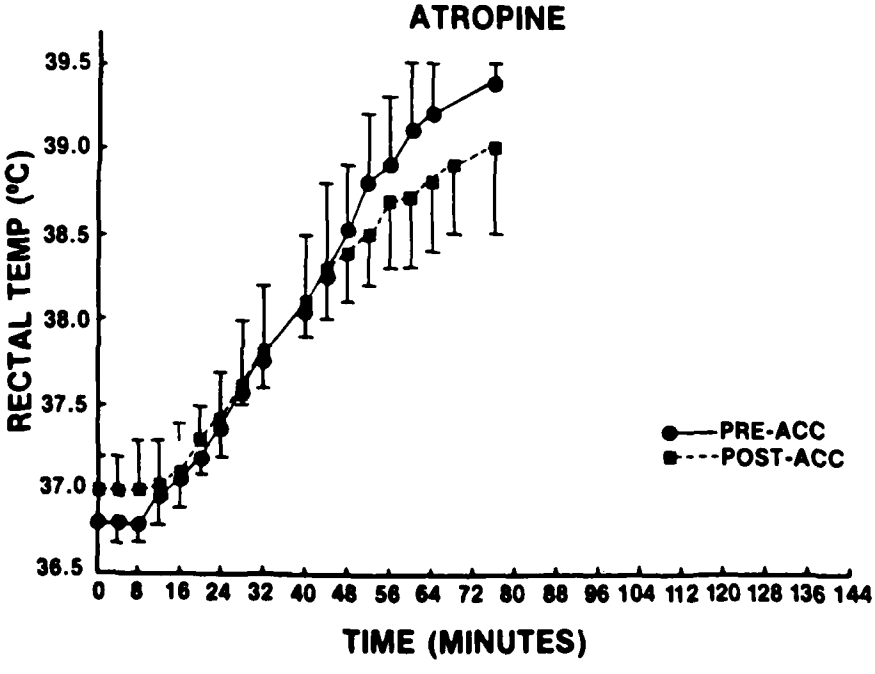

Figure 7. Rectal temperatures for conditions as described in figure 6 (n=7).

STUDY III

Methods

Subjects. Six healthy male volunteers participated as test subjects in this investigation after giving their informed their consent. The subjects, heat acclimated by standard procedures (23,37), were ($\bar{X}$ + SD): age, 22 $\pm$ 2 yrs; height, 176 $\pm$ 3 cm; weight, 78.8 $\pm$ 7.4 kg; Dubois body surface area, 1.95 $\pm$ 0.08 m^2 and percent body fat (12), 16.9 $\pm$ 3.6%.

Experimental Design. After completing the acclimation program, each subject performed two exercise-heat exposures in each of three environments of similar thermal stress: Hot-Dry (HD), T_{db} = 42.3°C, T_{dp} = 14.4 °C, rh = 20%, WBGT = 29.1°C; Warm-Moist (WM), T_{db} = 33.9°C, T_{dp} = 23.9 °C, rh = 56%, WBGT = 28.9°C; Warm-Wet (WW), T_{db} = 30.4°C, T_{dp} = 24.2 °C, rh = 69%, WBGT = 27.4°C. Immediately before the subjects entered the environmental chamber they were injected intramuscularly (vastus lateralis muscle) with 2 mg of atropine once for each different environment, and with an identical volume (1 ml) of normal saline as a control, once for each environment. Atropine trials were separated by at least four days.

Testing consisted of an exercise-heat exposure in which the subjects walked at 1.34 $m \cdot s^{-1}$ on a level motor-driven treadmill for a period of 100 min or until T_{re} reached 39.5°C, HR was equal to or greater than 180 $bt \cdot min^{-1}$ for 5 consecutive min, or the subject voluntarily removed himself from the test.

During testing, T_{re}, $\bar{T}_{sk}$ and HR were continuously measured. Metabolic heat production was calculated three times during each test (30, 60, 90 min) from open circuit spirometry measurements. Subjects drank water ad libitum during all heat exposures, and individual drinking patterns were charted during testing. Total body sweating rates were determined from body weight changes

(corrected for water ingested) measured with a Sauter balance prior to and immediately following the exercise-heat test. In order to determine local effects of atropine injection on the skin during each specific environmental exposure, we measured upper arm dew-point using automatic dew-point sensors (19). Arm sensible heat loss or gain (R+C, $W \cdot m^{-2}$) was determined from the arm convective heat transfer coefficient (h_c, $W \cdot m^{-2} \cdot K^{-1}$), a linear radiation heat transfer coefficient (h_r) and the gradient between arm skin temperature (T_{sk}, a) and the black globe temperature. We used an average local convective heat transfer coefficient of 7.3 $W \cdot m^{-2} \cdot K^{-1}$ (32). Local skin wettedness (18) was calculated continuously as $(P_{s,dpl} - P_w)/P_{s,sk} - P_w$ where: $P_{s,\ dpl}$ is the saturated vapor pressure (torr) of the arm dew-point sensor, and $P_{s,sk}$ is the saturated vapor pressure at arm skin temperature ($T_{sk,\ a}$).

Statistical Treatment. A two-way repeated measures analysis of variance (ANOVA) was utilized for all data at 35 min of exercise. ANOVA was also used to examine total exercise time as well as sweating rates among different tests. Stepwise regressions of the 35-min rectal temperature, total exposure time, total body weight, lean body mass (LBM), percent body fat, Dubois Surface Area (BSA), and surface area to weight ratio ($BSA \cdot wt^{-1}$) and anthropometric data were evaluated. Post hoc comparisons were made using the Tukey-Cramer method (39). Data presented are means $\pm$ SD.

Results

In the control experiments, all six subjects completed the tests (100 min) in all three environmental conditions. In the atropine experiments, exposure time was significantly less ($P<0.05$) than control in HD (73.5 min), but not in WM (90.2 min) or WW (100 min). Within atropine tests, exposure time in WW was greater ($P<0.05$) than in HD. In the HD test, only one subject completed the 100

min exposure. Two subjects were removed for elevated T_{re} (39.5°C), and the remaining three suffered syncope. Four subjects completed the atropine tests in WM. One subject was removed for elevated T_{re} and one due to syncope. All subjects completed the atropine test in WW. Time course responses in all environments for atropine and control are shown for T_{re} in Figure 8 and for HR in Figure 9.

Mean data for T_{re}, $\bar{T}_{sk}$, HR and M at the 35th min of exposure during each of the six experimental conditions are presented in Table 4. The 35th min was the last point in which data are available for all subjects during all conditions. Additionally, the 35th min approximates the time of highest circulating plasma levels of atropine after an intramuscular injection (27). Rectal temperature in HD was 0.6°C higher ($P<0.05$) during the atropine test compared to control. There were no significant differences in T_{re} between atropine and control tests in either WM or WW. Among the three atropine tests T_{re} was 0.6°C higher ($P<0.05$) in HD relative to WW. Skin temperatures during the atropine experiments were significantly higher ($P<0.01$) than during control in HD (3.9°C), WM (3.7°C) and WW (3.0°C). Since $\bar{T}_{sk}$ is driven by ambient temperature, it was significantly higher ($P<0.01$) with each higher ambient dry bulb condition within atropine and control tests. Heart rates during the atropine experiments were higher ($P<0.01$) than during control by 62 bt·min^{-1} in HD, 58 bt·min^{-1} in WM, and 45 bt·min^{-1} in WW. Among the atropine experiments the 35-min HR during WW was lower ($P=0.01$) than in either HD or WM. There were no significant differences among the three control trials. The metabolic rates at 35 min of exercise were not different between atropine and control experiments during any of the three environmental conditions.

Table 4. Mean (±S.D.) values for six subjects at the 35th minute of exercise in the three environments

	T_{re} (°C)	$\bar{T}_{sk}$ (°C)	ΔQ ($W \cdot h \cdot m^{-2}$)	$\dot{M}$ ($W \cdot m^{-2}$)	HR ($bt \cdot min^{-1}$)
Control					
HD	37.3 (0.1)	34.4Δ (1.1)	15.5 (6.9)	195 (19)	95 (7)
WM	37.4 (0.2)	33.1Δ (1.0)	19.6 (5.0)	184 (23)	90 (7)
WW	37.2 (0.1)	32.6Δ (0.5)	15.5 (9.0)	186 (7)	89 (8)
Atropine					
HD	37.9*† (0.3)	38.3Δ† (0.5)	38.2°† (7.0)	197 (16)	157† (10)
WM	37.5 (0.3)	36.8Δ† (0.6)	23.4 (10.5)	192 (16)	148† (12)
WW	37.3 (0.2)	35.6Δ† (0.4)	18.7 (4.4)	186 (13)	134**† (9)

* HD greater than WW ($P = 0.05$)
** WW less than HD and WM ($P < 0.05$)
° HD greater than WM and WW ($P < 0.05$)
† Atropine greater than control ($P < 0.05$)
Δ Each value significantly different from others within a treatment ($P < 0.01$)

Individual sweating rates for each trial are shown in Table 5. Following atropine treatment, sweating rates were lower ($P<0.01$) than those observed during the control tests by 5.5 $g \cdot min^{-1}$ in HD, 4.0 $g \cdot min^{-1}$ in WM and 3.4 $g \cdot min^{-1}$ in WW. Within the atropine experiments, sweating rate was 2.3 $g \cdot min^{-1}$ lower in WM compared to HD, and 1.1 $g \cdot min^{-1}$ lower in WW relative to WM ($P<0.01$). Among the control tests sweating rate was 3.8 $g \cdot min^{-1}$ lower in WM relative to HD, and 1.7 $g \cdot min^{-1}$ lower in WW than WM ($P<0.01$).

Table 5. Individual and mean (±S.D) sweating rates ($g \cdot min^{-1}$) for six subjects during exercise in the three environments

	HD		WM		WW	
	Control	Atropine	Control	Atropine	Control	Atropine
Subjects						
1	12.4	7.7	9.4	5.6	7.5	4.9
2	12.7	5.0	10.5	3.4	7.5	3.6
3	13.5	10.1	10.7	5.4	8.9	4.1
4	13.1	9.2	8.8	6.0	7.4	4.2
5	11.7	5.3	9.2	4.6	6.8	3.2
6	14.2	7.3	6.1	5.5	6.4	4.0
$\bar{X}$* *	12.9	7.4	9.1	5.1	7.4	4.0
S.D	(0.9)	(2.0)	(1.7)	(0.9)	(0.8)	(0.6)

* Mean values significantly different ($p < 0.01$) between each environmental condition for both control and atropine experiments.

* Mean values from atropine experiments significantly lower ($p < 0.01$) than control values at each environmental condition.

Figure 10 shows that a significant decrement in local skin wettedness occured following atropine injection. This inhibition of sweat gland function amounted to ~50% reduction at min 50 ($P < 0.05$) in comparison to control. The local skin wettedness in the control WW experiments was also higher ($P < 0.05$) than that present in the other two environments. A plot of local w as a function of ΔT_{re} from initiation of exercise to peak T_{re} (Fig. 11) confirms the fact that the slope was also higher during the experiments in the WW environment. There was no significant relationship between local w: ΔT_{re} in the atropine experiments.

Figure 12 demonstrates the effects of atropine and saline injection during exercise in the heat on arm sensible heat loss (R+C, $W \cdot m^{-2}$). The gradation in heat loss from this site is clearly evident; primarily, heat loss occurred in the WM and WW environments with atropine injection, a lessened R+C response in the WM environment following saline injection, and a definite heat gain response in the HD environment with both saline and atropine injection. At each time period, the arm R + C was significantly different between environments. This figure shows that during the atropine experiments, the response was always towards a greater heat loss than that in the control experiments.

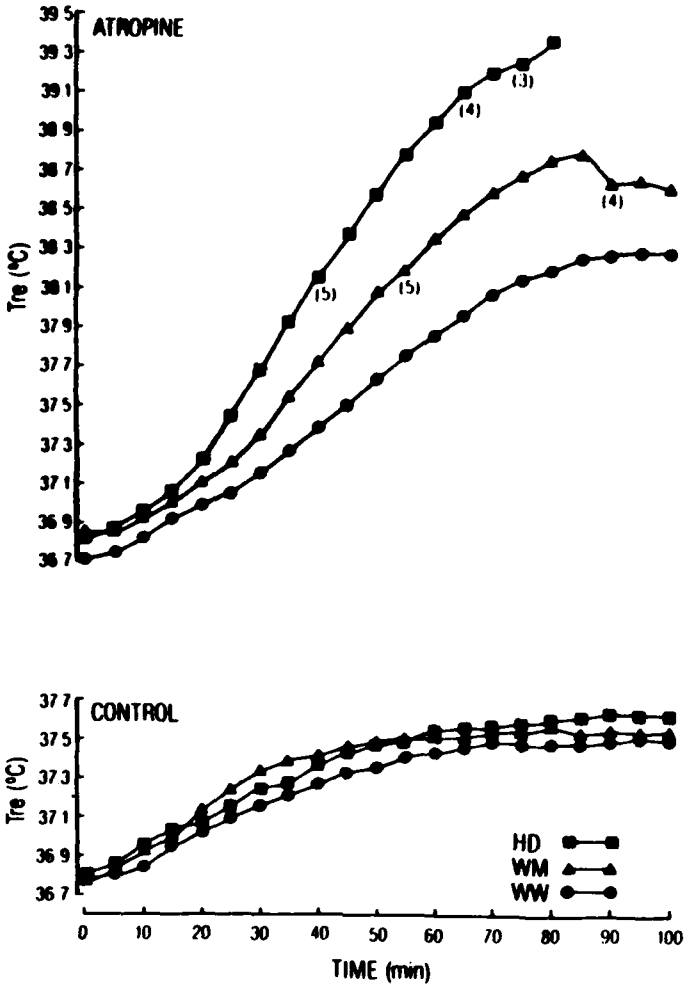

Figure 8. Mean rectal temperatures in each of three environments during atropine and control tests. n=6 except during atropine tests where subjects were removed during testing and group size is indicated by the number in parentheses.

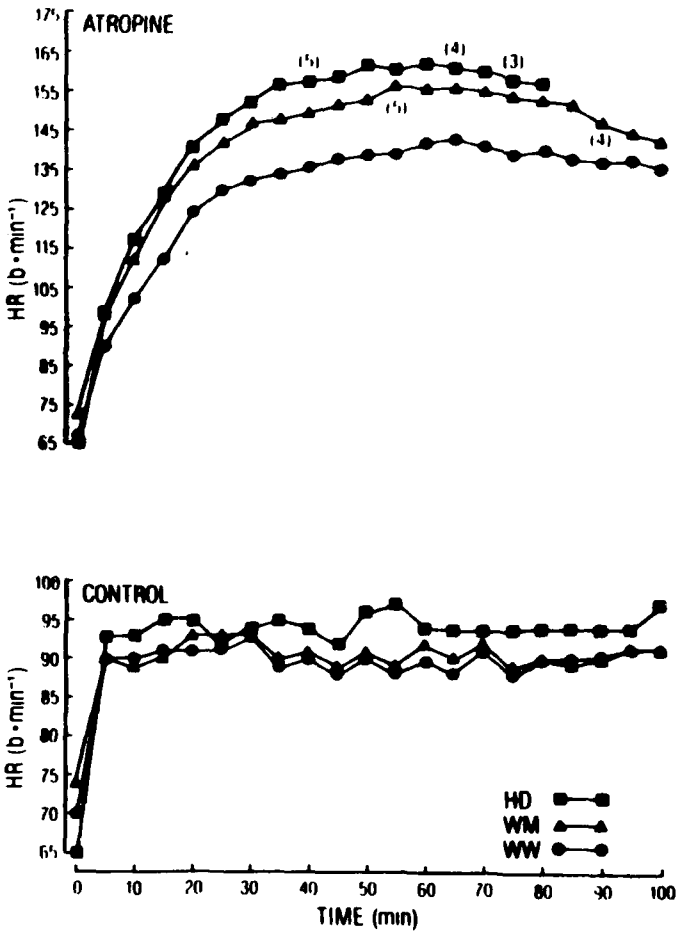

Figure 9. Mean heart rates for conditions and sample size as described in figure 8.

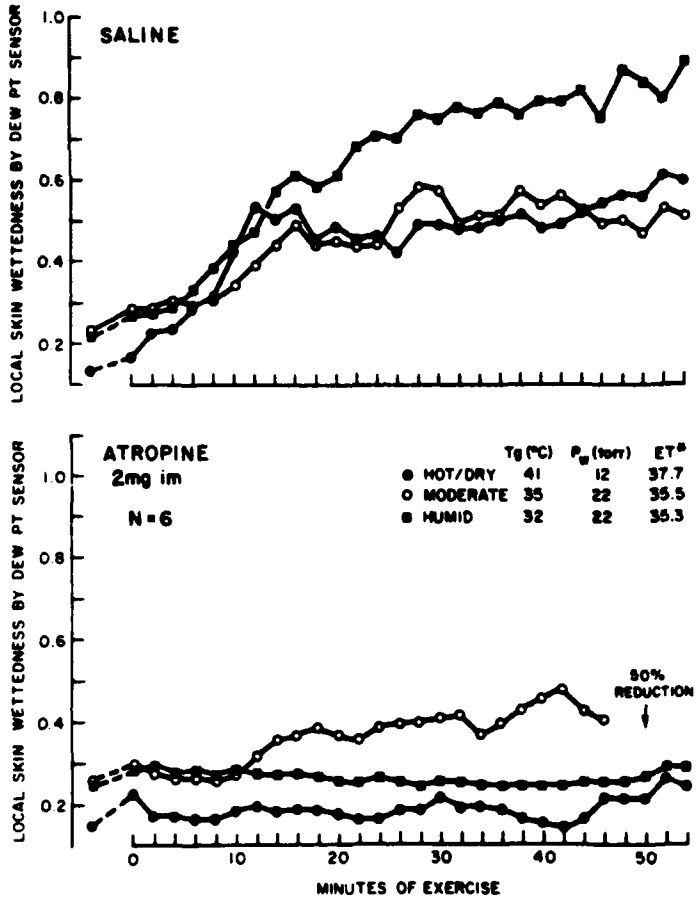

Figure 10. Local skin wettedness (w) of the upper arm, varying with time in the three environments. Reduction in w after atropine injection is significantly different ($p < 0.05$) from control experiments after min 30 in all three environments.

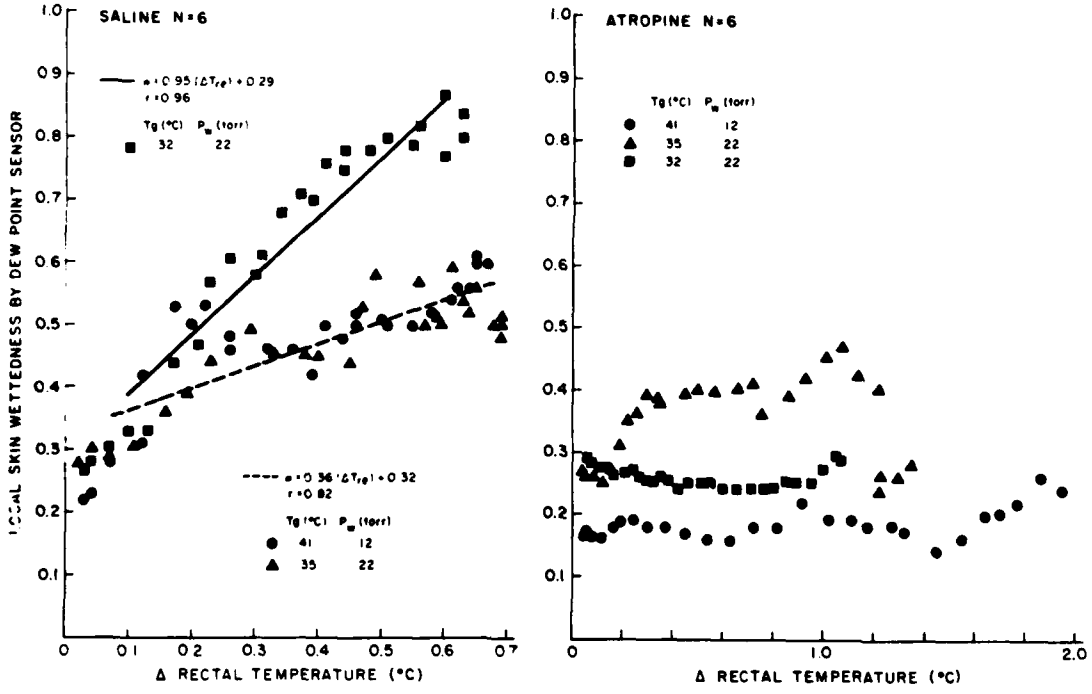

Figure 11. Local skin wettedness as a function of change in rectal temperature (ΔT_{re}) from the start of exercise.

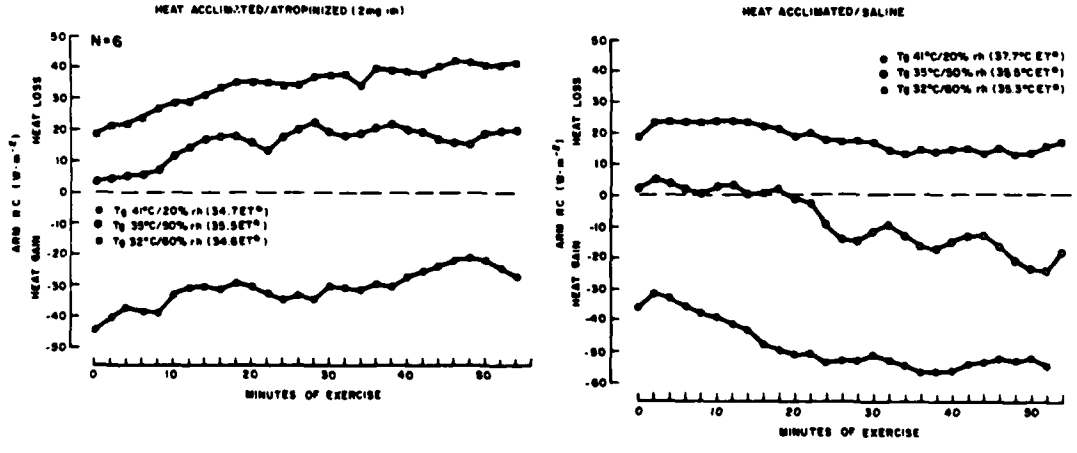

Figure 12. Arm dry heat loss (R + C) as a function of time of exercise.

DISCUSSION

Observations from these three studies have characterized the interaction of exercise-heat stress with thermoregulatory function in man. Data from the first study show a strong linear relationship between atropine dosage and elevated T_{re}. The 4 mg dosage of atropine caused approximately twice the absolute rise in core temperature as the 2 mg dosage. In contrast, the increased HR with atropine (due to vagal inhibition) was nearly maximal with a 2 mg dosage; there was little, if any, further increase in HR with 4 mg. Results from the first study also indicate that atropine treatment had no influence on subsequent control tests. From the results of the two 2 mg trials, there was little evidence of a cumulative effect of the drug.

The second study provides evidence that heat acclimation can increase the length of time men injected with 2 mg atropine can exercise in a hot-dry environment where evaporative heat loss is the primary heat exchange mechanism (3,14,31,36). This study demonstrated the decrement in sweating rate with 2 mg of atropine administration, which resulted in the increased heat storage observed. The probable mechanism for the increased endurance time in heat-acclimated subjects treated with atropine is potentiation of sweat gland secretion and ensuent evaporative cooling. The greater efferent drive to the sweat gland in heat-acclimated subjects resulted in an increased acetylcholine concentration, which competed with atropine at the effector junction (3,14), and possibly an increased cholinergic sensitivity of the eccrine sweat gland (35). Therefore, thermoregulatory sweating can occur more readily (as evidenced by higher sweating rates), in subjects treated with atropine following heat acclimation, enabling greater cooling and longer exercise-heat exposures post-

acclimation. The increased sweating rates and lower skin temperatures in heat-acclimated, atropine-treated subjects are consistent with this hypothesis (Table 1).

In the third study, while the WBGT index was similar in all experiments, the HD environment had the greatest evaporative capacity (E_{max}) and the least opportunity for dry (sensible) heat loss; whereas the WW had the lowest E_{max}, but a favorable gradient for sensible heat loss.

Sweating rates were suppressed by about 45% in atropinized subjects in all three environments. This reduction in evaporative cooling was most critical in HD where skin to ambient temperature gradient ($\bar{T}_{sk}$-T_a) was unfavorable to sensible heat loss, ultimately leading to increased T_{re} and decreased exercise performance. Atropine's similar suppression of sweating in WM was not as debilitating for the subjects. The lack of evaporative cooling led to $\bar{T}_{sk}$ above T_a and a gradient favorable to sensible heat loss, leading to reduced heat storage and less of a decrement in exercise performance than in HD. In contrast, during the control test in this environment, evaporatve heat loss provided the primary mechanism for cooling. In the WW environment, the 45% suppression of sweating in the atropine test was of little consequence to the subjects' ability to thermoregulate. The low water vapor pressure gradient between saturated skin and the air provided for little evaporative heat loss regardless of the drug treatment. In WW during the atropine test the $\bar{T}_{sk}$-T_a gradient was greatest, resulting in the least increase in T_{re}. Consequently, this was the only test environment in which all subjects were able to complete the exercise performance during the atropine test.

The strong (> 50%) inhibition of sweat gland activity as demonstrated by a suppressed local skin wettedness response, despite a heat acclimation state, was

accompanied by a concurrent compensatory cutaneous heat loss as shown by changes in R+C (Fig. 11). Our data do not directly reveal whether the increase in cutaneous blood flow following injection of atropine was attributable to reflex release of skin arteriolar tone by cholinergic vasodilator influences (5), or was related to elevation in skin temperature attributed to changes in R+C which thermally oppose diminished sweating. Since changes in R+C were higher in the environments where skin blood flow is potentiated by release of vasoconstrictor activator, the initial "atropine flush" may be related to a mechanism primarily in response to immediate and diminished sweat gland activity. This study showed that atropine injection in heat-acclimated subjects at three discrete environmental conditions caused similar inhibition in sweating, but differential local heat reponses (R+C).

While these studies were not designed to determine the time course for physiological effects of atropine administration, it was noted that in Study I, peak HR were recorded after 50 min of exercise in all atropine trials, and in Study II peak HR and maximal effect on sweating rates were noted after approximately 30-35 min of heat exposure. These results are consistent with previous studies, which note 30-60 min as the time course for maximum effect on HR and sweating rate (9,10,21,26,29,33,34).

SUMMARY

In summary, observations from these three studies were:

Study I

1. The relationship between T_{re} and atropine dosage was linear, while the relationship between HR and atropine dosage was curvilinear (HR tended to plateau at higher dosages).
2. Rectal temperatures (in subjects with or without atropine) were not altered by previous days of atropine administration.
3. A 0.5 mg dosage of atropine resulted in elevated HR and $\bar{T}_{sk}$.

Study II

4. Prior exercise-heat acclimation reduced the rate of heat storage during exercise exposure to hot-dry environmental conditions, and increased performance time.
5. This decreased heat storage comes from enhanced sweating resulting in better heat dissipation in acclimated individuals treated with atropine.

Study III

6. Atropine administration impeded thermoregulation most in the hot-dry environment where cooling depended primarily on evaporative heat loss, and where the potential for sensible heat loss was negligible (14,31).
7. In environments enabling dry heat loss, atropine's effect on thermoregulation was minimal.

References

1. Borg, G. Perceived exertion as an indicator of somatic stress. Scand. J. Rehabil. Med. 2:92-98, 1970.

2. Brownlee, K.A. Statistical theory and methodology in science and engineering. New York: John Wiley and Sons, Inc., 1960.

3. Bullard, R.W., M.R. Banerjee, F. Chen, R. Elizondo and B.A. MacIntyre. Skin temperature and thermoregulatory sweating: a control systems approach. In: Hardy, J.D., ed. Physiological and behavioral temperature regulation. Springfield, IL: Thomas: 597-610, 1970.

4. Burton, A.C. Human calorimetry II. The average temperature of the tissues of the body. J. Nutr. 9:261-280, 1935.

5. Celander, O. and B. Folkow. The correlation between the stimulation frequency and the dilator response evoked by "antidromic" excitation of the thin afferent fibres in the dorsal roots. Acta Physiol. Scand. 29:371-390, 1953.

6. Clubley, M., C.E. Bye, T. Hensen, A.W. Peck and C. Riddington. A technique for studying the effects of drugs on human sweat gland activity. Eur. J. Clin. Pharmacol. 14:221-226, 1978.

7. Craig, F.N. Effects of atropine, work and heat on heart rate and sweat production in man. J. Appl. Physiol. 4:826-833, 1952.

8. Craig, F.N., E.G. Cummings, H.L. Froelich and P.E. Robinson. Inhibition of sweating by atropine before and after acclimatization to heat. J. Appl. Physiol. 27: 498-502, 1969.

9. Cullumbine, H. and S. Miles. The effect of atropine sulphate on men exposed to warm environments. Q. J. Exp. Physiol. 41: 162-179, 1956.

10. Cullumbine, H., W.H.E. McKee and N.H. Creasey. The effects of atropine sulphate upon healthy male subjects. Q.J. Exp. Physiol. 40: 309-319, 1955.

11. Custance, A.C. and C.A. DeCandole. A *pilot study of the suppressive* effects of three dosages of atropine upon the sweating mechanism of four male subjects during moderate exercise. Defense Research Chemical Laboratories Report No. 427. Ottawa, Canada, 1964.

12. Durnin, J.V.G.A. and J. Womersley. Body fat assessed from total body density and its estimate from skinfold thickness measurements on 481 men and women aged 16-72 years. Br. J. Nutr. 32:77-97, 1974.

13. Eichna, L.W., C.R. Park, N. Nelson, S.M. Horvath and E.D. Palmes. Thermal regulation during acclimation in a hot dry (desert type) environment. Am. J. Physiol. 163:585-597, 1950.

14. Elizondo, R.S. Local control of eccrine sweat gland function. Fed. Proc. 32:1583-1587, 1973.

15. Gagge, A.P. Partitional calorimetry in the desert. In: Yousef, M.K., S.M. Horvath and R.W. Bullard, eds. Physiological adaptations to desert and mountain. New York: Academic Press: 23-51, 1972.

16. Gagge, A.P., J.A.J. Stolwijk and J.D. Hardy. Comfort and thermal sensations and associated physiological responses at various ambient temperatures. Environ. Res. 1: 1-20, 1967.

17. Gonzalez, R.R., L.G. Berglund and A.P. Gagge. Indices of thermoregulatory strain for moderate exercise in the heat. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 44(6): 889-899, 1978.

18. Gonzalez, R.R. and K. Cena. Evaluation of vapor permeation through garments during exercise. J. Appl. Physiol. 58:928-935, 1985.

19. Graichen, H., R. Rascati and R.R. Gonzalez. Automatic dew-point temperature sensor. J. Appl. Physiol.: Repirat. Environ. Exercise Physiol. 52:1658-1660, 1982.

20. Headley, D.B. Effects of atropine sulfate and pralidoxime chloride on visual, physiological, performance, subjective, and cognitive variables in man: A Review. Milit. Med. 147: 122-132, 1982.

21. Kalser, S.C. and P.L. McLain. Atropine metabolism in man. Clin. Pharmacol. Ther. 11: 214-227, 1970.

22. Kolka, M.A., W.L. Holden and R.R. Gonzalez. Heat exchange following atropine injection before and after heat acclimation. J. Appl. Physiol.:Respirat. Environ. Exercise Physiol. 56: 896-899, 1984.

23. Kolka, M.A., L. Levine, B.S. Cadarette, P.B. Rock, M.N. Sawka and K.B. Pandolf. Effects of heat acclimation on atropine-impaired thermoregulation. Aviat. Space Environ. Med. 55:1107-1110, 1984.

24. Leithead, C.S. and A.R. Lind. Heat stress and heat disorders. London: Cassell, 1964.

25. Levine, L., M.N. Sawka, B.E. Joyce, B.S. Cadarette and K.B. Pandolf. Varied and repeated atropine dosages and exercise-heat stress. Eur. J. Appl. Physiol. 53: 12-16, 1984.

26. Marzulli, F.N. and D.P. Cope. Subjective and objective study of healthy males injected intramuscularly with 1, 2 and 3 mg atropine sulfate. Medical Division Research Report No. 24. Army Chemical Center, MD, 1950.

27. Metcalfe, R.F. A sensitive radioreceptor assay for atropine in plasma. Biochem. Pharm. 30: 209-212, 1981.

28. Meyers, F.H., E. Jawatz and A. Goldfien. Medical pharmacology. Los Altos, CA: Lange Medical Publications:71-79, 1980.

29. Mirakhur, R.K. Comparative study of the effects of oral and i.m. atropine and hyoscine in volunteers. Br. J. Anaesth. 50: 591-598, 1978.

30. Montagna, W. Histological, histochemical and pharmacological properties. In: Montagna, W., ed. Advances in biology of the skin, Vol III. Eccrine sweat glands and eccrine sweating. New York: Pergamon Press: 6-29, 1962.

31. Nadel, E.R., C.B. Wenger, M.F. Roberts, J.A.J. Stolwijk and E. Cafarelli. Physiological defenses against hyperthermia of exercise. Ann. N.Y. Acad. Sci. 301:98-109, 1977.

32. Nishi, Y. and A.P. Gagge. Direct evaluation of convective heat exchange by napthalene sublimation. J. Appl. Physiol 29: 830-838, 1970.

33. Robinson, S. The physiological effects of atropine and atropine substitutes. Medical Laboratories Contract Report No. 15. Army Chemical Center, MD, 1953.

34. Robinson, S., M. Pearcy, R.E. Buckingham, J.H. Smith, W. Daly, R. Maletich, D. Miller and D. Robinson. The effects of varying doses of atropine on temperature regulation of working men. Medical Laboratories Contract Report No. DA 18-108-CML 2397. Army Medical Center, MD, 1952.

35. Sato, K and F. Sato. Individual variations in structure and function of human eccrine sweat gland. Am. J. Physiol. 245: R203-R208, 1983.

36. Sawka, M.N., L.Levine, M.A. Kolka, B.S. Appleton, B.E. Joyce and K.B. Pandolf. Effect of atropine on the exercise-heat performance of man. Fundam. Appl. Toxicol. 4: S190-S194, 1984.

37. Sawka, M.N., M.M. Toner, R.P. Francesconi and K.B. Pandolf. Hypohydration and exercise: effects of heat acclimation, gender, and environment. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 55(4): 1147-1153, 1983.

38. Snedecor, G.W. and W.G. Cochran. Statistical methods, 7th edition. Ames, IA: Iowa State University Press: 274-279, 1980.

39. Sokal, R.R. and F.J. Rohlf. Biometry, 2nd edition. San Francisco: W.H. Freeman and Co.: 507-509, 1981.

40. Weir, J.B. DeV. New methods for calculating metabolic rate with special reference to protein metabolism. J. Physiol. 109: 1-9, 1949.

41. Winsmann, F.R., C.K. Bensel, R.F. Goldman and K.B. Pandolf. Physiological and subjective evaluation of the temperate battle dress uniform (TBDU) and three other uniforms worn by men and women in tropical climatic conditions. U.S. Army Research Institute of Environmental Medicine, Technical Report No. T4/83. Natick, MA, 1983.

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